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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,045	11/13/2001	Timothy R. Brazelton	286002021300	8147

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,045	BRAZELTON ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13,15-17 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1,4-13,15-17 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/9/2005 has been entered.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims, and a shift in claimed invention will not be reiterated. The arguments in 5/9/2005 and 2/2/06 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1, 4-13, 15-17, and 21, in the paper submitted 2/2/06 is acknowledged. The traversal is on the ground(s) that the Examiner appears to have already conducted a search with respect to the subject matter of the pending claims and sifted the available prior art because several references and a host review articles cited discussing stroke and other vascular disorders. This is not found persuasive because each type of disease causing the neurodegeneration has distinct etiology, and pathogenesis, belong to different disease

category, require different technical considerations, and would not overlap in a structured search. When considering technical aspects of stem cell therapy, there are issues that are common to many types of disorders, but publication addressing one aspect of the issue in no way can replace a thorough search and consideration of another distinct disease. The review articles may have sampled various area of stem cell therapy, but an overview cannot replace a though search of prior art on a particular disorder. Thus it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent methods of treating distinct disorders. The search may be overlap but not co-extensive. Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the divergent search criteria. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1, 4-13, 15-17, 21, 35 are pending, however, claims 35 is withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1, 4-

13, 15-17, 21 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-13, 15-17, 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering bone marrow-derived cells to the brain of a subject via intravenous administration of unfractionated (whole) bone marrow cells, wherein said cells acquired neuronal cell phenotype months after transplantation, wherein the recipient subject has been lethally irradiated, does not reasonably provide enablement for treating a neuronal deficiency caused by Parkinson's disease with any fraction of BM-derived cells, to a recipient that has not undergone BM preconditioning, and by any route of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction

provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are drawn to treating a neuronal deficiency comprising administering bone marrow-derived cells by vascular administration to an individual having a neuronal deficiency caused by Parkinson's disease, wherein the cells are from self or an allogenic origin, wherein at least one symptom of the neuronal deficiency are ameliorated. Given the broadest reasonable interpretation, the claimed method is drawn to treating Parkinson's disease in humans.

In view of the disclosure of the specification, it contemplates a method for treating neuronal deficiency with bone marrow-derived cells, it provides an extensive list of various diseases that may cause neuronal deficiency, it teaches preparing mouse whole bone marrow cells genetically marked for transplantation, it teaches lethally irradiating an isogeneic recipient before transplantation, and it teaches at 8-12 weeks after transplantation, multiple neuronal cell surface markers could be detected in the implanted cells. However, the specification fails to teach the functional aspect of the cells, whether cells bearing a few neuronal cell markers would also have the function of neuronal cells, particularly in the case of treating Parkinson's disease, whether cells bearing a few neuronal cell markers would secret dopamine, and to the extend it ameliorates a symptom of the disease.

In May 9, 2005, five years after the priority date, the applicant submitted a declaration providing additional experimental data showing that bone marrow transplantation into MPTP-treated and lethally irradiated mice increased the number of tyrosine hydroxylase dopaminergic neurons in the substantia nigra and dopamine transporter immunoreactivity in the striatum compared to control group. The declaration also discloses there was significantly improved motor performance of the BM-transplanted MPTP-injured mice. However, it is noted the specification as filed never contemplates the MPTP-treated mouse model, nor reasonably predicts the BM cells in the brain would provide neuronal cell function. Apparently, the data disclosed in the declaration is an addition to the original disclosure, and clearly the enablement of the instant claims is relied on the post-filing date data. The applicant is reminded that the court has ruled (*In re Glass*, 181 USPQ 31, (CCPA 1974)), IF A DISCLOSURE IS INSUFFICIENT AS OF THE TIME IT IS FILED, IT CANNOT BE MADE SUFFICIENT, WHILE THE APPLICATION IS STILL PENDING BY LATER PUBLICATIONS WHICH ADD TO THE KNOWLEDGE OF THE ART SO THAT THE DISCLOSURE, SUPPLEMENTED BY SUCH PUBLICATIONS, WOULD SUFFICE TO ENABLE THE PRACTICE OF THE INVENTION. INSTEAD, SUFFICIENCY MUST BE JUDGED AS OF THE FILING DATE; SECTION 132 PROHIBITS ADDING NEW MATTER TO DISCLOSURE AFTER FILING". In *In re Glass*, the appellant attempted to use the disclosures of four patents issued after his filing date, and court ruled, "IF INFORMATION TO BE FOUND ONLY IN SUBSEQUENT PUBLICATIONS IS NEEDED FOR SUCH ENABLEMENT, IT CANNOT BE SAID THAT THE DISCOSURE IN THE APPLICATION EVIDENCES A COMPLETED INVENTION... IT IS AN APPLICANT'S OBLIGATION TO SUPPLY ENABLING DISCLOSURE WITHOUT RELIANCE ON WHAT OTHERS MAY PUBLISH AFTER HE HAS FILED AN APPLICATION ON WHAT IS SUPPOSED TO BE A COMPLETED INVENTION", "IF HE CANNOT SUPPLY ENABLING INFORMATION, HE IS

NOT YET IN A POSITION TO FILE. Without the post-filing data, the specification fails to support the full scope of the claimed invention.

Further, the nature of the Parkinson's disease makes it difficult to model and treat. Parkinson's disease (PD) is a neurodegenerative disorder of middle or late life, with very gradual progression and a prolonged course. The precise etiology or mechanism of progression is unknown. To this end, the specification fails to provide an enabling disclosure for what is now claimed even if one includes the post-filing date data because the MPTP-toxin PD model does not fully correlates with the human Parkinson's disease. *Fleming et al* (NeuroRx 2005;2:495-503) teaches, "TRADITIONAL TOXIN MODELS OF PD HAVE FOCUSED ON THE NIGROSTRIATAL PATHWAY AND THE LOSS OF DOPAMINE NEURONS IN THIS REGION, AND THESE MODELS HAVE BEEN IMPORTANT IN OUR UNDERSTANDING OF PD AND IN THE DEVELOPMENT OF SYMPTOMATIC TREATMENTS FOR THE DISEASE. HOWEVER, THEY ARE LIMITED IN THAT THEY DO NOT REPRODUCE THE FULL PATHOLOGY AND PROGRESSION SEEN IN PD" (abstract). Here since the mouse model differs from human PD in many different levels, it is highly unpredictable whether the functional improvement observed in a mouse model could be seen in a human subject suffering from PD.

This position is supported by the skilled artisan in the pertinent art. For example, *Hows* (Trans Immunol 2005;14:221-3) reviewed many remain questions in the art with respect to treating PD with adult bone marrow stem cells, such as which fraction of marrow stem cells is the most important pool of stem cells, whether said cells directly or indirectly contribute to an improved function, how the intravascular administered cells might home from the circulation to the target tissue, how to prevent tumor formation of the transplanted stem cells, etc.; and teach "THERE HAS BEEN A RECENT SURGE OF INTEREST

IN THE THERAPEUTIC POTENTIAL OF ADULT HUMAN STEM CELLS. MUCH OF THE PUBLISHED WORK IS CONTRADICTORY EMPHASIZING THE NEED FOR CONTINUED HIGH QUALITY RESEARCH ON THE MOLECULAR AND CELLULAR PROCESSES INVOLVED BEFORE PROCEEDING TO ATTEMPTING THE CLINICAL APPLICATION OF ADULT MARROW STEM CELL THERAPY FOR DEGENERATIVE DISEASE AND TO REPAIR TISSUE DAMAGE ON A LARGE SCALE" (last paragraph, page 223, emphasis added).

From a different perspective, the claimed invention is highly unlikely to be enabled because it calls for autologous bone marrow-derived cell transplantation. To this end, how one explains the fact that a PD patient has normal bone marrow-derived cells, yet PD still arises and progresses in the patient? To this end, any reasonable skilled would not comprehend how simply transplanting the bone marrow cells of a PD patient back to the patient would treat neuronal deficiency of the PD. Hence, based on a common sense, transplanting autologous bone marrow from a PD patient to treat PD is unlikely to be successful. And one cannot simply extrapolate from a mouse model to predict the same treatment strategy would work in humans. Accordingly, the claimed invention is unlikely to be enabled at current levels of the skill to ameliorate a symptom of the PD in a human patient.

The claimed invention encompasses transplanting the BM-derived cells to a recipient without lethal irradiation. It is well known and a routine practice in the art when bone marrow transplantation is involved, a preconditioning step is required to lethally or non-lethally ablate the recipient bone marrow to provide space for the transplant and to prevent immune rejection response. Both the specification and the post-filing date data use lethally irradiated recipient for transplantation, it is highly unpredictable whether the bone marrow-derived cells would engraft and homing to brain tissue and be able to

successful in phenotypic transition to neuronal cell type. Accordingly, the specification fails to provide an enabling disclosure commensurate with the scope of the claims.

The claimed invention encompasses and the specification contemplates transplanting a fractionated population of bone marrow-derived cells. However, the specification fails to teach which fraction is effective in neuronal progenitor cell homing and phenotype transformation. As *Hows* indicates, such knowledge was still not available long after instant priority date. Here, specific but not general guidance is required. The specification fails to shed light on this aspect, and thus fails to provide an enabling disclosure to support the full scope of the claimed invention.

The claims broadly encompass any vascular delivery of BM-derived cells. The working example of the specification uses tail vein infusion. It is noted although it seems that any number of means can deliver the BM-derived cells to circulation, the results are not always predictable. For example, it is known in the art certain tumor metastatic model may be established only by intravenous delivery but not via artery system. Factors yet unknown may influence the traveling pattern, homing, and engraftment of implanted cells. The disclosure only provides enablement for intravenous delivery.

Accordingly, in view of the quantity of experimentation necessary to determine the outcome of bone marrow transplantation in PD patients, and at therapeutic levels, in particular for the treatment of PD, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to functional aspect of the engrafted cells in the brain, and the breadth of the claims directed to the treatment of Parkinson's Disease with any fraction of bone marrow-derived cells, it

would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

It is noted that the applicant appears to be the first to disclose a novel means of delivering bone marrow cells to the brain through intravenous route as opposed to direct brain tissue delivery, and provides evidence that these cells acquired neuronal cell surface markers while homing and residing in the brain (*Brazelton et al*, Science 2000, IDS). Accordingly, the applicant may be entitled for a patent drawn to such a method of delivery BM-derived cells to the brain.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1, 4-13, 15-17, 21 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Claims 1, 4-13, 15-17, 21 are directed to an invention not patentably distinct from claims 1-21 of commonly assigned U.S. patent application 10/688,747. Specifically, claims of co-pending application embrace instant claims.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned application, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly

assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-13, 15-17, 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 of copending Application No. 10/688,747. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are drawn to a species of the genus, i.e. treating a neuronal deficiency caused by anyone of many diseases, including a Parkinson's Disease.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
March 6, 2006